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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,830	01/30/2002	Yizhong Gu	PB0169	3442

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,830	GU, Y. ET AL	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *13-31,34-38 and 40-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,32,33 and 39* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election without traverse of Invention I, Claims 1-12, 32, 33, and 39 in Paper No. 9 is acknowledged. Claims 13-31, 34-38, and 40-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected Inventions, there being no allowable generic or linking claim.

Specification-Objections

The specification is objected to for a typographical error on page 52, line 14 wherein "...(ii) a degenerate variant of SEQ ID NO: 7..." should be "...(ii) a degenerate variant of SEQ ID NO: 6...". Correction is required.

The specification is objected to for a typographical error on page 143, Table 3; "mytonic" should be "myotonic". Correction is required.

Abstract

The abstract is objected to for not defining the term "LCP". Correction is required.

Claims-Objections

Claim 1 is objected to for reciting the phrase "...diseases involving cell-cell adhesion process...". Said phrase should be corrected to either "...diseases involving a cell-cell adhesion process..." or "...diseases involving cell-cell adhesion processes...".

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 fails to further limit Claim 1, from which is depends. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12, 32, 33, and 39 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

As stated in the specification, the proposed utilities for the recited nucleic acid molecules and the encoded LCP proteins are in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process (pg 5, line 31 -pg6, line 2). These asserted utilities for the recited polynucleotides are not specific as, an extremely large number of human DNAs are associated with neurological and developmental disorders, as well as diseases involving a cell-cell adhesion.

The disclosure more specifically states that the LCP gene and encoded proteins are associated with the autosomal recessive deafness disease DFNH9 and/or myotonic dystrophy 2 (Table 3). The evidence for LCP being involved in DFNH9 is that the LCP gene maps to a region of the human chromosome, 3q12.1, within the region, 3q, for DFNH9 (Table 3) and the questionable logic that mutation in the LCCL-domain of another protein causes DFNH9 (pg 143, line 23-26). The fact that this other LCCL-containing protein, COCH, maps to the locus for DFNH9 and individuals with DFNH9 have mutations within the LCCL domain of COCH, has led to the conclusion that said mutations of COCH are responsible for DFNH9 (Roberston et al, 1998; cited in the specification). The fact that LCP has a LCCL domain, maps near the locus for DFNH9, and that mutation within the LCCL domain of another protein causes DFNH9 is not

sufficient evidence to conclude a credible role for LCP in DFNH9. Applicant's assertion that LCP plays a role in myotonic dystrophy 2 is based simply on the fact that this disease also maps to the 3q region of the human chromosome (Table 3). Again, the correlation between the location for LCP gene and myotonic dystrophy 2 is not sufficient to be convinced of a credible role for LCP in this disease especially in light of the fact that other diseases, for example, DFNH9 maps to the same regions. These proposed utilities for the LCP gene and encoded proteins are not supported by any demonstrated function for the recited polynucleotides and proteins in either DFNH9 or myotonic dystrophy 2. Furthermore, these asserted utilities are not supported by a deduced function for said polynucleotides and proteins, as evidenced by the function of known LCP proteins, for example, in non-human species. Thus, these asserted utilities for the recited polynucleotides are neither specific as, a large number of human DNAs are associated with any region of the chromosome nor credible as no demonstrated or deduced function has been has been shown. Without such evidence, a utility for LCP in the diagnosis and/or treatment of DFNH9 and/or myotonic dystrophy 2 is not credible.

The specification also proposes that the recited nucleic acids have utility as hybridization probes, (pg27, line 12), for anti-sense inhibition of expression (pg29, lines 1-2), bound to substrates (pg35, lines 15-20), in microarrays (pg38, line 31), to prime synthesis of nucleic acids (pg42, lines 23-26), for cDNA-mRNA subtraction (pg44, line 31), for in vitro translation (pg44, line 31-32), to express the encoded protein (pg45, lines 3-5), to target homologous recombination (pg 48, lines 4-6), and as commercial products (pg48, line2-3). Each of these utilities is an application which would apply to every member of a general class of materials and/or is a use only for further research to determine a use for the recited nucleic acid molecules or the proteins

encoded thereby. As such, these asserted utilities are not specific (for those applicable to all human DNAs) or not substantial because the use of the recited polynucleotides therein is only potential and not in currently available in practical form.

Therefore, Claims 1-12, 32, 33, and 39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a deduced or an established utility.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 32, 33, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "conservative amino acid substitutions" which is not defined in the specification. Although very common in the art, the term "conservative substitution" is vague and indefinite. For example, is a Gln/Glu substitution or an Asp/Asn substitution conservative? Are Ser/Tyr and Phe/Tyr conservative substitutions? Another situation that is indefinate is the classification of Gly and Ala; are these small polar residues, similar to Ser, Thr, Gln and Asn, or hydrophobic? Is His basic or hydrophobic? Are linear hydrophobic amino acids similar to aromatic hydrophobic amino acids? Is Cys a small polar amino acid or its own category? Is Tyr a polar amino acid or an aromatic amino acid? Lack of consensus on the answers to these questions causes the term "conservative substitution" to be indefinite. Therefore, Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Since Claims 2-12, 32, 33, and 39 are dependent on Claim 1, they are also rejected under 35 U.S.C. 112, second paragraph for the reasons described above.

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 is unclear in reciting the phrase "or the progeny thereof". Claim 11 could recite either the progeny of the host cell or the progeny of the nucleic acid molecules of Claims 1 or 8-10. Therefore, Claim 11 and Claim 12, which is dependent on Claim 11, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Clarification is required. For purposes of examination, it is assumed that Claim 11 recites the progeny of the host cell.

Claim 1 is unclear in reciting "SEQ ID NO: 2, 1113" and "SEQ ID NO: 3, 1114". Claim 1 should be amended to recite "SEQ ID NO: 2 or SEQ ID NO: 1113" and "SEQ ID NO: 3 or SEQ ID NO: 1114.

For clarity in Claim 4, "SEQ ID NO: 4, 6 or 1115" should be amended to recite. "SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 1115"

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 32, 33, and 39 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a convincing asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if applicants show a specific, substantial, and credible utility for the polynucleotides encoding SEQ ID NO: 4, 6, or 1115, the following rejection will apply. Claims 1-12, 32, 33, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acids of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 1113 and polynucleotides encoding the polypeptides set forth by SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 1115, and/or the complement thereof and/or degenerate variant thereof, does not reasonably provide enablement for nucleic acids encoding polypeptides comprising any number of any conservative amino acid substitutions of the polypeptides set forth by SEQ ID NO: 3 and SEQ ID NO: 1114. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Claim 1 is so broad as to encompass any polynucleotide sequence that encodes a protein which is involved in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process wherein said protein has any number of conservative amino acid substitutitons of the polypeptides set forth by SEQ ID NO: 3 and SEQ ID NO: 1114. The scope of this claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired involvement in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are

conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to nucleic acids of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 1113 and the polypeptides set forth by SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 1115.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claim 1 which, encompasses any polynucleotide sequence that encodes a protein which is involved in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process wherein said protein has any number of conservative amino acid substitutions of the polypeptides set forth by SEQ ID NO: 3 and SEQ ID NO: 1114. The specification does not support the broad scope of Claim 1 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the role in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process; (B) the general tolerance of the role in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D)

the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Since Claims 2-12, 32, 33, and 39 further recite probes, microarrays, vectors, host cells methods of expressing the nucleic acids of Claim 1, and compositions comprising the nucleic acids of Claim 1, Claims 2-12, 32, 33, and 39 are also rejected under 35 U.S.C. 112 first paragraph due to lack of enablement for the same reasons discussed above.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of polynucleotides encoding any polypeptide with an enormous number of amino acid modifications of the proteins of SEQ ID NO: 3 and SEQ ID NO: 1114 wherein said polypeptides are involved in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-12, 32, 33, and 39 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of DNA molecules encoding any polypeptide with an enormous number of amino acid modifications of the proteins of SEQ ID NO: 3 and SEQ ID NO: 1114 wherein said polypeptide is involved in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process. The specification teaches the structure of only three representative species of such DNAs. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protein involved in neurological and developmental disorders, as well as diseases involving a cell-cell adhesion process. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Birren et al, 2000 or Rosteck et al, 2000, or Hillier et al, 1995. Birren et al teach a polynucleotide (EMBL #

AC013497) that has 100% identity with SEQ ID NO: 4 over 140 nucleotides and 100% identity with SEQ ID NO: 6 over 275 nucleotides. Rosteck et al teach a polynucleotide that has 100% identity with SEQ ID NO: 4 over 300 nucleotides and 100% identity with SEQ ID NO: 6 over 257 nucleotides. Hillier et al teach a polynucleotide that has 100% identity with SEQ ID NO: 1115 over 60 nucleotides, the full-length.

Claim 4 is rejected under 35 U.S.C. 102(e) as being anticipated by Penn et al, 2001. Penn et al teach a polynucleotide that has 100% identity with SEQ ID NO: 6 over 275 nucleotides, the full-length.

Therefore, Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Birren et al, 2000 or Rosteck et al, 2000, or Hillier et al, 1995 and under 35 U.S.C. 102(e) as being anticipated by Penn et al, 2001.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birren et al, 2000 or Rosteck et al, 2000, or Hillier et al, 1995 or Penn et al, 2001 in view of Old et al, 1985 and Schena et al, 1996. The teachings of Birren et al, Rosteck et al, Hillier et al, and Penn et al, are described above. Neither Birren et al, Rosteck et al, Hillier et al, nor Penn et al, teach their nucleotides detectably labeled, attached to a substrate, or in a microarray. However, to label nucleic acids (Old et al, Fig 6.4) as well as attach nucleic acids to a substrate and use them in

microarrays is common in the art (Schena et al, pg10614 parg 5) and it would have been obvious to a person of ordinary skill in the art to do so with the polynucleotides of Birren et al, Rosteck et al, Hillier et al, Penn et al. The use of the methods of Old et al, 1985 to label the nucleotides of Birren et al, Rosteck et al, Hillier et al, Penn et al, is suggested by Old et al wherein, they state that a labeled probe allows hybridization analysis of any population of sequences (page 119, parg 2). The use of the methods of Schena et al to attach the nucleotides of Birren et al, Rosteck et al, Hillier et al, Penn et al, to a substrate and use said nucleotides in a microarray is suggested by Schena et al wherein the describe the value of microarrays for analysis of gene expression (page 10614, paragraph 2). Motivation to use the methods of Old et al or Schena et al to label or attach the polynucleotides of Birren et al, Rosteck et al, Hillier et al, Penn et al to a substrate in a microarray derives from the ability to use said labeled and attached polynucleotides to detect DNA and RNA having the same or complementary sequence. The expectation of success is high as, labeled polynucleotides and polynucleotides attached to substrates in a microarray are common in the art. Therefore, Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birren et al, 2000 or Rosteck et al, 2000, or Hillier et al, 1995 or Penn et al, 2001 in view of Old et al, 1985 and Schena et al, 1996.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1600